PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A23L 1/29, 1/30, A61K 35/78 | A1

(11) International Publication Number: **WO 99/62358**

(43) International Publication Date: 9 December 1999 (09.12.99)

(21) International Application Number: PCT/KR99/00271

(22) International Filing Date: 2 June 1999 (02.06.99)

(30) Priority Data:
1998/20560 3 June 1998 (03.06.98) KR

(71) Applicant *(for all designated States except US)*: KOREA RESEARCH INSTITUTE OF BIOSCIENCE AND BIOTECHNOLOGY [KR/KR]; 52, Oeun-dong, Yuseong-gu, Daejeon 305-333 (KR).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BOK, Song, Hae [KR/KR]; Garam Apt., 15-1202, Samcheon-dong, Seo-gu, Daejeon 302-222 (KR).

(74) Agents: JANG, Seong, Ku et al.; KEC Building, 17th floor, 275-7, Yangjae-dong, Seocho-ku, Seoul 137-130 (KR).

(81) Designated States: CA, CN, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: HEALTH-IMPROVING FOOD COMPOSITION COMPRISING GINSENG AND CITRUS PEEL DERIVATIVE

(57) Abstract

A food composition for improving health, comprises ginseng and a citrus peel derivative selected from the group consisting of a flavonoid found in citrus peel, a citrus peel extract and a mixture thereof, wherein the weight ratio of ginseng and the citrus peel derivative ranges from 1:1 to 1,000:1.

[redacted]

ATTORNEY DOCKET NUMBER:11592-006-999
SERIAL NUMBER: 10/088,664
REFERENCE: **B23**

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

HEALTH-IMPROVING FOOD COMPOSITION COMPRISING GINSENG AND CITRUS PEEL DERIVATIVE

FIELD OF THE INVENTION

The present invention relates to a health-improving food composition comprising ginseng and a citrus peel derivative.

BACKGROUND OF THE INVENTION

Ginseng, Panax schin-seng, is an oriental medicinal herb having excellent health-promoting effects. For example, it relieves fatigue, enhances physical strength, stabilizes the cardio-circulatory, nerve and digestive systems, and prevents diabetes. Accordingly, ginseng is presently employed in a variety of health-improving foods, cosmetic and herbal medicine composition(Hong moonwha, An Explanatory Interpretation of Huh Joon's Dongeuibogam, 396-398(1990)).

However, it is known that ginseng does not lower the plasma cholesterol level and it is not effective in preventing cardio-circulatory diseases, e.g., atherosclerosis and hypercholesterolemia, which have increasingly become a major cause of deaths. Therefore, it is desirable that a ginseng product is supplemented with a component that has plasma cholesterol-lowering activity.

It is known that the flavonoids extracted from citrus peel, e.g., naringin, naringenin, hesperidin and hesperetin, have activities in improving lipid metabolism to prevent cardio-circulatory diseases, as well as anticancer and antiviral activities. In particular, it has been reported that both hesperidin and hesperetin have capillary-enhancing, permeability-reducing, anti-platelet aggregation, anti-inflammation, anti-viral, and blood pressure- and cholesterol-lowering activities(Meyer, O. C., Angiology, 45,

579-584(1994); Struckmann, J. R., et al., Angiol., 45, 419-428(1994); Matsubara, Y., et al., Japan Organic Synthesis Chem. Association Journal, 52, 318-327(1994. Mar.); Galati, E. M., et al., Farmaco., 51(3), 219-221(1996, Mar.); Monforte, M. T., et al., Farmaco., 50(9), 595-599(1995, Sep.); JP 95-86929; JP 95-86930; Chung, M. I., et al., Chin. Pharm. J.(Taipei)., 46, 429-437(1994, Nov.); Galati, E. M., et al., Farmaco., 40(11), 709-712(1994, Nov.); and Emim, J. A., et al., J. Pharm. Pharmacol., 46(2), 118-122(1994)). Further, it has been reported that both naringin and naringenin have anti-cancer, anti-ulcer, and cholesterol-lowering activities(Monforte, M. T., et al., Farmaco., 50(9), 595-599(1995, Sep.); JP 95-86929; JP 95-86930; Felicia, V., et al., Nutr. Cancer, 26, 167-181(1996); EP 0352147 A2(1990.1.24); and Martin, M. J., et al., Parmacol., 49, 144-150(1994)).

However, there have been reported no ginseng composition containing a citrus peel derivative that has beneficial effects such as cholesterol-lowering activity. The present inventor has endeavored to develop an health-improving food composition comprising ginseng and have discovered that a food composition containing ginseng and a citrus peel derivative in effective in preventing adult diseases such as cancer, hypertension and cardio-circulatory diseases.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a food composition for improving health.

In accordance with one aspect of the present invention, there is provided a food composition for improving health, which comprises ginseng and a citrus peel derivative selected from the group consisting of a flavonoid found in from citrus peel, a citrus peel extract and a mixture thereof, wherein the weight ratio of ginseng and the citrus

peel derivative ranges from 1:1 to 1,000:1.

DETAILED DESCRIPTION OF THE INVENTION

Ginseng may be used in the present invention in the form of unprocessed fresh ginseng or a processed ginseng product, e.g., dried ginseng, steamed red ginseng, a ginseng extract, ginseng powder, ginseng drink and ginseng tea.

A citrus peel derivative which may be used together with ginseng in the present invention is any one or more of the flavonoids extracted from citrus peel, a citrus peel extract or a mixture thereof.

The flavonoids obtainable from citrus peel include naringin, naringenin, hesperidin and hesperetin. These flavonoids may be extracted from citrus peel or synthesized according to the processes described by Zemplen, Bognar, Ber., 75, 1043(1943) and Seka, Prosche, Monatsh., 69, 284(1936). Further, naringenin and hesperetin can be prepared by the hydrolysis of naringin and hesperidin, respectively.

The citrus may be tangerine, orange, lemon, citron, grapefruit and Poncirus trifoliata.

The citrus peel extract may be prepared by any of the conventional methods using an alcohol or water. For instance, 5 to 100 ℓ of ethanol or water is added to 1 kg of dried citrus peel and the mixture is allowed to stand at a temperature ranging from 5 to 140 °C for water for a period ranging from 10 min. to 48 hours. This extraction step may be repeated 1 to 3 times. The resulting extract is concentrated, e.g., by vacuum, to obtain a concentrated peel extract. Further, it can be prepared by treating citrus peels with a calcium hydroxide or sodium hydroxide solution at a temperature of 25 to 60 °C for 1 to 5 hours, adding hydrochloric acid thereto to adjust the solution pH to 4.0 to 7.0, and then standing the resulting solution at 4 °C for 10 to 48 hours to obtain precipitated flavonoids.

The inventive composition comprising ginseng and citrus peel derivative exerts health-improving effects, i.e., it prevents diabetes and cardio-circulatory diseases, relieves the fatigue, enhances physical strength, stabilizes cardio-circular, nerve and digestive systems. The prevention for cardio-circulatory diseases is accomplished partly by lowering the total plasma cholesterol level while elevating the HDL-cholesterol content. This beneficial effect of the inventive composition is notable in view of the fact that ginseng alone does not lower the total plasma cholesterol level or raise the HDL-cholesterol content. Further, the prevention for cardio-circulatory disease is achieved partly by inhibiting the activity of 3-hydroxy-3-methylglutaryl CoA(HMG-CoA) reductase, a regulatory enzyme of the cholesterol synthesis in the liver, which is remarkable in view of the fact that ginseng alone enhances HMG-CoA reductase activity.

Moreover, in spite of its potent efficacies, citrus peel derivatives show little toxicity or mitogenicity in animal tests. More specifically, citrus peel derivatives exhibit no toxicity when they are orally administered to mice at a dose of 100 mg/kg, which corresponds to an oral administration dose of 3 to 10 g/kg body weight of the citrus peel derivative for a person weighing 50 kg. Further, the citrus peel derivative exerts no adverse effects on the liver function.

The health-improving food composition of the present invention may further include flavors, vitamins, preservatives, exipients, carriers, and other edible additives.

The health-improving food composition of the present invention may be formulated in the form of powder, capsule, pill, tablet or drink according to any of the conventional procedures.

The food formulation of the present invention may be taken daily in a typical citrus peel derivative dose of

about 10 to 500 mg/kg body weight, preferably 20 to 100 mg/kg body weight, and can be taken in a single dose or in divided doses.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Further, percentages given below for solid in solid mixture, liquid in liquid, and solid in liquid are on a wt/wt, vol/vol and wt/vol basis, respectively, and all the reactions were carried out at room temperature, unless specifically indicated otherwise.

Example 1: Preparation and Analysis of Citrus Peel Extract

Citrus peel was dried at room temperature and added to 6.7kg of the dried peel was 80 ℓ of 95% ethanol. The mixture was allowed to stand at room temperature for 24 hours and filtered to obtain an extract and a solid residue. The solid residue was extracted one more time by the same procedure. The extracts thus obtained were combined, concentrated under a reduced pressure using a large capacity evaporator(EYELA Rotary vacuum evaporator N-11) to obtain 1.7 kg of a concentrated extract(d=1.3g/ml).

The concentrated extract was dissolved in a DMSO/methanol(1:1) mixture to a concentration of 10 mg/ml. 100μl of the resulting solution was subjected to high performance liquid chromatography(HPLC) using Phenomenex Prodigy column(5μ ODS(3) 100Å, 4.6x250mm) which was pre-equilibrated with 0.01M phosphoric acid/methanol(70:30) mixture. The sample was eluted with a mixture of 0.01M phosphoric acid and methanol(70:30) for 55 min. at a flow rate of 0.6 ml/min while gradually increasing the methanol content to 45%. 100μl(1mg/ml) samples of hesperidin and naringin(Sigma Chemical Co., USA) were used as standard materials. The eluates were detected at 280nm and it was discovered that 1kg of the citrus peel extract contained

5,950mg of hesperidin and 280mg of naringin.

Further, ingredients of the citrus peel extract were identified in accordance with conventional methods. For instance, moisture content was determined by dry method at 105°C; crude protein, by Kjeldahl method; crude lipid, by Soxhlet method; free saccharide, by Bertrand method; crude ash, by ashing at 550-600°C; and hesperidin and naringin, by HPLC method. The result is shown in Table I.

Table I

Ingredient		Content(%)
Moisture		39.1
Crude protein		2.7
Crude lipid		1.8
Free saccharide	Fructose	20.0
	Glucose	16.5
	Sucrose	8.6
Crude ash		1.0
Hesperidin		0.6
Naringin		0.03
Other saccharides		9.67

Example 2: Administration of a Mixture of Naringin and Ginseng to an Animal

40 four-week-old Sprague-Dawley rats(Taihan laboratory animal center, Korea) each weighing about 90 to 110 g were evenly divided into four dietary groups by a randomized block design. The rats of the four groups were fed with four different high-cholesterol diets, i.e., AIN-76 laboratory animal diet(ICN Biochemicals, Cleveland, OH, U.S.A.) containing 1 % cholesterol(Control group); 1 % cholesterol plus 0.1 % naringin(Naringin group); 1 % cholesterol plus 0.1 % ginseng(Ginseng group); and 1 %

cholesterol plus 0.1 % naringin plus 0.1 % ginseng(Naringin plus Ginseng group), respectively. The compositions of diets fed to the four groups are shown in Table II.

Table II

Dietary group / Ingredient	Control group	Naringin group	Ginseng group	Naringin plus Ginseng group
Casein	20	20	20	20
D,L-methionine	0.3	0.3	0.3	0.3
Corn starch	15	15	15	15
Sucrose	49	48.9	48.9	48.8
Cellulose powder*	5	5	5	5
Mineral mixture*	3.5	3.5	3.5	3.5
Vitamin mixture*	1	1	1	1
Choline bitartrate	0.2	0.2	0.2	0.2
Corn oil	5	5	5	5
Cholesterol	1	1	1	1
Naringin	-	0.1	-	0.1
Ginseng	-	-	0.1	0.1
Total	100	100	100	100

* Purchased from TEKLAD premier Co.(Madison, WI, U.S.A.)

The rats were allowed to feed freely on the specified diet together with water for six weeks, the ingestion amount was recorded daily and the rats were weighed every 7 days, and then the record was analyzed. All rats showed a normal growth rate and there was observed no significant difference among the four groups in terms of the feed ingestion amount and the weight gain.

Example 3: Determination of Total Cholesterol, HDL-Lipid Content in Plasma

The effect of administering a mixture of naringin and ginseng to rats on the plasma cholesterol and neutral lipid content was determined as follows.

Blood samples were taken from the rats of the four dietary groups of Example 2 and plasma HDL fractions were separated therefrom by using HDL-cholesterol reagent(Sigma Chemical Co., Cat. No. 352-3) containing dextran-sulfate. Total cholesterol and HDL-cholesterol levels were determined by using Sigma Diagnostic Kit Cat. No. 352-100(Sigma Chemical Co., U.S.A.)(Allain et al., Clin. Chem., 20, 470-475(1974)). Neutral lipid level was determined by using Sigma Diagnostic Kit Cat. No. 339-50(Bucolo, G. and David, H., Clin. Chem., 19, 476-482(1973)). The result in Table III shows that the total plasma cholesterol levels of the rats of the naringin plus ginseng group is lower by 25 % than that of the control group, while those of the naringin and ginseng groups are by 18 % and 9 % lower than that control, respectively.

Table III

Group / Lipid Conc.	Control group	Naringin group	Ginseng group	Naringin plus Ginseng group
Total-C (mg/dl)	148.01 ±9.80	120.98 ±5.45	134.99 ±5.09	110.50 ±5.10
HDL-C (mg/dl)	25.71 ±2.11	29.67 ±2.53	22.84 ±2.15	29.10 ±3.10
$\frac{\text{HDL-C}}{\text{Total-C}}$ (%)	17.5	25.6	17.1	26.3

* Total-C: Total-cholesterol
* HDL-C: HDL-cholesterol

Example 4: Activity of a Mixture of Naringin and Ginseng in HMG-CoA Reductase Inhibition

(Step 1) Preparation of microsomes

To determine the effect of feeding a mixture of naringin and ginseng to rats on the activity of HMG-CoA reductase, a regulatory enzyme of the cholesterol synthesis in the liver, microsomes were separated from the liver tissue to be used as an enzyme source.

First, the rats of the four groups prepared in Example 2 were sacrificed by decapitation and their livers were excised. 2 g each of the livers was homogenized in 6 ml of homogenization medium(0.1 M triethanolamine, 0.02 M ethylenediamine tetraacetic acid(EDTA)(pH 7.4), 2 mM dithiothreitol(DTT)). The homogenate was centrifuged at 10,000xg for 10 min. at 4°C and the supernatant thus obtained was centrifuged at 12,000xg for 10 min. at 4°C to obtain a supernatant. The supernatant was put in an ultracentrifuge tube(Beckman) and centrifuged at 100,000xg for 1 hour at 4°C to obtain microsomal pellets, which were then suspended in 2 ml of the homogenization medium and centrifuged at 100,000xg for 1 hour at 4°C. The pellets thus obtained were suspended in 1 ml of the homogenization medium. The concentration of proteins in the resulting suspension was determined by Bradford's method and then adjusted to 4 to 8 mg/ml. The resulting suspension was stored in a deep freezer(Biofreezer, Forma Scientific Inc.).

(Step 2) HMG-CoA reductase assay

The activity of HMG-CoA reductase was determined by employing [^{14}C]HMG-CoA, in accordance with the method of Shapiro et al.(Biochemica et Biophysica Acta, 370, 369-377(1974)) as follows.

The enzyme in the supernatant containing the microsome

obtained in (Step 1) was activated at 37°C for 30 min. Added to a reaction tube were 20 μl of HMG-CoA reductase assay buffer(0.25M KH_2PO_4(pH 7.0), 8.75 mM EDTA, 25 mM DTT, 0.45 M KCl and 0.25 mg/ml BSA), 5 μl of 50 mM NADPH, 5 μl of [^{14}C]HMG-CoA(0.05 μCi/tube, final conc. 120 μM), and 10 μl of activated microsomal enzyme(0.03-0.04 mg), and the mixture was incubated at 37°C for 30 min. The reaction was terminated by adding 10 μl of 6 M HCl to the mixture, and the mixture was incubated at 37°C for 15 min. to allow complete lactonization of the product(mevalonate). The precipitate was removed by centrifugation at 10,000xg for 5 min. and the supernatant was applied to a Silica gel 60F_{254} TLC plate(Merck & Co., Inc., Germany) and then developed with benzene:acetone(1:1, v/v). A region having a Rf value ranging from 0.3 to 0.6 was identified using Image Analyger(MacBas 1000, Fuji, Japan) and removed by cutting and assayed for radioactivity with Packard Tricarb 1600TR Scintillation counter(Packard, Australia). Enzyme activities were calculated as picomoles mevalonic acid synthesized per min. per mg protein(pmoles/min/mg protein). The result is shown in Table IV.

Table IV

Group	Control group	Naringin group	Ginseng group	Naringin plus Ginseng group
HMG-CoA reductase activity (pmole/min/mg protein)	111.04 ±9.87	83.79 ±12.33	146.28 ±24.36	90.10 ±13.1

As can be seen from Table IV, the control group rats show a relatively high HMG-CoA reductase activity, and the HMG-CoA activity observed with the ginseng group is higher than that of the control group, while those of the naringin

group and naringin plus ginseng group are lower than that of the control group.

Example 5: Toxicity of Orally Administered Citrus Peel Derivative

7 to 8 week-old, specific pathogen-free ICR female mice(8 heads) each weighing about 25 to 29 g and male mice(8 heads) each weighing about 34 to 38 g were bred under the condition of temperature 22±1°C, moisture 55±5% and photoperiod 12L/12D. Fodder(Cheiljedang Co., mouse and rat fodder) and water were sterilized and fed to the mice.

Naringin, hesperidin or a citrus peel extract was dissolved in 0.5% Tween 80 to a concentration of 100 mg/ml, and the solution was orally administered to the mice in an amount of 0.2 ml per 20 g of mouse body weight. The solution was administered once and the mice were observed for 10 days for signs of adverse effects or death according to the following schedule: 1, 4, 8, and 12 hours after the administration and, every 12 hours thereafter. The weight changes of the mice were recorded every day to examine the effect of the citrus peel derivative. Further, on the 10th day, the mice were sacrificed and the internal organs were visually examined.

All the mice were alive at day 10 and the citrus peel derivative showed no toxicity at a dose of 1,000 mg/kg. The autopsy revealed that the mice did not develop any pathological abnormality, and no weight loss was observed during the 10 day test period. Accordingly, it was concluded that the citrus peel extract is not toxic when orally administered to an animal.

Example 6: Preparation of Food composition containing Ginseng and Citrus Peel Derivative

Food compositions containing a mixture of ginseng and

a citrus peel derivative, i.e., naringin, naringenin, hesperidin, hesperetin, citrus peel extract, or a mixture thereof, were prepared as follows.

(1) preparation of a health-improving capsule

Hard gelatin capsules were prepared using the following ingredients:

	Quantity
ginseng powder	150 mg
citrus peel derivative	100 mg
jujube, honey or raisin powder	100 mg
vitamin C	50 mg
lactose	100 mg
total	500 mg

The above ingredients were mixed and filled into hard gelatin capsules in 500 mg/unit quantities.

(2) preparation of a health-improving pill

Pills, each containing 500mg of the following composition, were prepared.

ginseng powder	150 mg
citrus peel derivative	100 mg
jujube, honey or raisin powder	100 mg
vitamin C	50 mg
Carboxymethylcellulose	100 mg
total	500 mg

(3) preparation of a health-improving tablet

Tablets, each containing 500mg of the following

composition, were made as follows:

	Quantity
ginseng powder	150 mg
citrus peel derivative	100 mg
jujube, honey or raisin powder	100 mg
vitamin C	50 mg
Carboxymethylcellulose	50 mg
starch or lactose	30 mg
magnesium stearate	20 mg
total	500 mg

Ginseng power, citrus peel derivative, and starch or lactose were passed through a No. 45 mesh U.S. sieve and mixed thoroughly. Water was mixed with the resultant powder mixture, and then passed through a No. 14 mesh U.S. sieve. The granules so produced were dried at 50 °C and passed through a No. 18 mesh sieve. Carboxymethylcellulose, vitamin C and magnesium stearate, previously passed through a No. 60 mesh U.S. sieve, were then added to the granules, which after mixing, were compressed on a tablet machine to yield tablets weighing 500 mg each.

(4) preparation of a health-improving drink

100 g of fresh ginseng was washed with water, and 100 ml of water and 1 g of sugar were added thereto and blended to obtain a ginseng juice. 100 ml of the ginseng juice was mixed with 100 mg of hesperidin or hesperetin together with 20 mg of vitamin C to obtain a health-improving drink.

(5) preparation of a health-improving drink

The procedure of (4) was repeated except that instead of hesperidin or hesperetin either naringin or naringenin was used while vitamin C was omitted.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

What is claimed is:

1. A food composition for improving health, which comprises ginseng and a citrus peel derivative selected from the group consisting of a flavonoid found in citrus peel, a citrus peel extract and a mixture thereof, wherein the weight ratio of ginseng and the citrus peel derivative ranges from 1:1 to 1,000:1

2. The food composition of claim 1, wherein the ginseng is fresh ginseng, dried ginseng, steamed red ginseng, a ginseng extract, ginseng powder, ginseng drink or ginseng tea.

3. The food composition of claim 1, wherein the citrus is tangerine, orange, lemon, citron, grapefruit and Poncirus trifoliata.

4. The food composition of claim 1, wherein the flavonoid is naringin, naringenin, hesperidin or hesperetin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00271

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: A 23 L 1/29, 1/30; A 61 K 35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: A 23 L 1/00, 2/00; A 61 K 35/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, PAJ, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 547 671 A (DUTHINH), 20 August 1996 (20.08.96), totality.	1-4
X	JP 06-128 165 A (TSUMURA & CO), 10 May 1994 (10.05.94), (abstract). [online][retrieved on 18 August 1999].Retrieved from: EPO WPI Database.	1-4
X	CN 1 082 355 A (ZHU), 23 February 1994 (23.02.94) (abstract). [online][retrieved on 18 August 1999].Retrieved from:EPO WPI Database.	1-4
X	CN 1 079 987 A (NANFENG INST.), 29 December 1993 (29.12.93) (abstract).[online][retrieved on 18 August 1999]. Retrieved from :EPO WPI Database.	1-4
X	CN 1 093 915 A (YIMIN PHARM.), 26 October 1994 (26.10.94) (abstract).[online][retrieved on 18 August 1999]. Retrieved from:EPO WPI Database.	1-4

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 1999 (23.08.99)	03 September 1999 (03.09.99)

Name and mailing adress of the ISA/AT	Authorized officer
Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200	Irmler Telephone No. 1/53424/133

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00271

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 1 179 969 A (FANGRUI), 29 April 1998 (29.04.98) (abstract). [online][retrieved on 18 August 1999]. Retrieved form:EPO EPODOC Database.	1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 99/00271

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A 5547671	20-08-1996	AU A1 63912/96 CA AA 2229796 EP A1 951761 WO A1 9710835	09-04-1997 27-03-1997 08-07-1998 27-03-1997
JP A2 6128165	10-05-1994	keine - none - rien	
CN A 1079987	29-12-1993	keine - none - rien	
CN A 1082355	23-02-1994	keine - none - rien	
CN A 1093915	26-10-1994	keine - none - rien	
CN A 1179969	29-04-1998	keine - none - rien	